DETAILED ACTION

1. This action is in response to the papers filed April 6, 2011. Currently, claims 1, 5, 7-28 are pending. Claims 5, 14-28 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection.

5. In view of the amendments to the claims and the interview held on October 13, 2010, Applicant has switched their election of the invention to the combination of all SNPs shown in Table 2. Applicant acknowledges this election in the remarks by stating "Applicant has amended claim 1 to require identifying in the nucleic acid sample nucleotide occurrences of the eye color related SNPs shown in Table 2".

Priority

6. This application is a 371 of PCT/US05/004513, filed February 11, 2005 and claims benefit of 60/544,788, filed February 13, 2004 and 60/548,370, filed February 27, 2004.

It is noted that although both elected SNPs of SEQ ID NO: 3 and 4, rs1004611 and rs1874835 are mentioned in the provisional applications, neither of the disclosures teach how to infer an eye color based upon an allele. There is no teaching which allele is associated with which eye color.

It is noted that not all of the SNPs provided in Table 2, as now claimed, are presented in the provisional applications. For example, Table 2 contains SEQ ID NO: 26, 32-40 and 44-48 that do not appear to be in either provisional application.

Response to Arguments

The response asserts that one of skill in the art would understand how to infer eye color based upon an allele in view of Example 1 of PCT/US05/004513. Applicant has also included a scientific article authored by the inventor to support inference of eye color. This argument has been considered but is not convincing because the response fails to points to any teachings of how to infer eye color in the provisional applications. The provisional applications do not provide any teachings of allele and how to infer eye colors.

With respect to the Frudakis article, the article provides a table which provides genes and SNPs that are "marginally associated with iris pigmentation" (see page 2075). Looking at SEQ ID NO: 29, for example in the OCA2 gene, the HWE-P value is

0.81 which is not a significant p-value. The Table provides no guidance as to what one would infer in the event that a G was determined.

With respect to the SNPs not found in the provisional applications and not found in the publication, there is no guidance how to infer natural eye color of a human based upon these SNPs.

The instant claims do not receive benefit to the February 13, 2004 or February 27, 2004 provisional applications.

Drawings

7. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 7-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the SNPs at each of the positions in Table 2, does not reasonably provide enablement for a method of inferring natural eye color in a human subject based upon detecting each of the SNPs of Table 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of inferring natural eye color in a human subject based upon detecting each of the SNPs in Table 2. Table 2 contains 32 SNPs.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the organization and sequence of the human P gene (Lee et al. Genomics, Vol. 26, pages 354-363, 1995). Mutations of the p gene result in type II oculocutaneous albinism (OCA2) in humans. Lee teaches the human OCA2 locus is mapped to 15q11-q13.

The OCA2 gene was formerly called the P gene.

Rebbeck et al. (Cancer Epidemiology, Biomarkers and Prevention, Vol. 11, pages 782-784, August 2002) teaches the p gene is an inherited biomarker of human eye color. Rebbeck teaches individuals were less likely to have blue or gray eyes if they had P gene variants (abstract). Rebbeck teaches eye color may be blue, gray,

green, hazel, light brown, dark brown and black. Rebbeck use the following categories of eye color for analysis bleu/gray; green/hazel and brown/black (page 782, col. 2).

Frudakis et al. (Genetics, Vol. 165, pages 2071-2083, December 2003) teaches identifying numerous SNPs, haplotypes and diplotypes within OCA2, for example associated with iris color. The list of SNPs in Table 2 do not include the SNPs of SEQ ID NO: 3 and 4. Frudakis teaches haplotypes with 13 different SNPs that appear to be associated with various distinghuishment of colors. For example sequence 1 of OCA2 distinguished blue from brown. And sequence 22 distinguishes green from blue. There are 6 haplotypes that do not distinguish any iris colors. For haplotypes as large as 13 SNPs, there are numerous combinations that fail to provide any guidance for iris color determination.

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher. The high level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with phenotypes. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, physiological state, or drug metabolism or response. Lucentini (The Scientist; 2004, Vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a

disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1 st complete paragraph). In the instant case, the specification only provides information that the variant exists, but provides no guidance that it has any effect whatsoever on the CYP 1A1 gene, expression, or activity, let alone any potential diagnostic or therapeutic effect

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification.

The specification provides no evidence that one of skill in the art could infer natural eye color of a human by detecting each of the 32 SNPs in Table 2. The specification teaches measuring iris colors with a cannon digital camera. 100 samples were collected. The specification teaches grouping the lightest 21 samples together and then grouping the darkest 21 samples together. The specification analyzes the samples for SNPs. 27 SNPs were used for further analysis. The specification teaches classification models incorporated 32 SNPs from Table 2. Table 2 comprises 32 SNPs. Table 3 lists 10 SNPs that were particularly useful for inferring eye color and indicates the eye color shade that can be drawn for a particular allele. SEQ ID NO: 3 T is listed as darker and SEQ ID NO: 4 T is listed as darker. The specification teaches darker indicates brown or hazel eyes while lighter indicates blue or green eyes (page 26). The specification teaches that iris colors of 'unknown" samples based on the genotypes of **35** SNPs provided a blind classification accuracy of 97% when an exact match existed across all of the gentoypes in Table 2. This seems to state that iris color could be inferred correctly 97% of the time if ALL 35 SNPs were correct. However Table 2, as claimed, is directed to only 32 SNPs. This provides no indication how to infer eye color based upon the presence of these 32 SNPs. Even more, there is no guidance what the "correct" color for the majority of the SNPs is. For example, SEQ ID NO: 26 is not found in Table 3 and Table 2 provides no indication of what eye color is associated with what allele. The specification states that the iris colors of known subjects may be used as a guide, however, the specification fails to provide a guide for each of the SNPs in Table 2 (para 59). The guidance provided by the specification amounts to an invitation for the

skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to allow the skilled artisan to infer natural eye color of a human by detecting the 32 SNPs of Table 2. The specification appears to state that for a 97% accuracy, it takes 35 SNPs to match across all genotypes. The specification does not provide any discussion of what type of accuracy one might expect with the use of only 32 SNPs.

Even more, the specification is silent with respect to a vast number of SNPs. As noted above, SEQ ID NO: 26, for example, does not appear to have any indication of which alleles are associated with which particular iris color. It is unclear if an A, T, C or G is associated with light or dark eye color. The specification states that the iris colors of known subjects may be used as a guide, however, the specification fails to provide a guide for each of the SNPs in Table 2.

Moreover, it is unclear how the skilled artisan would infer eye color in the event ALL SNPs "were not correct". For example, if nucleotide 68 of SEQ ID NO: 3 were to indicate a darker eye shade and nucleotide 171 of SEQ ID NO: 4 were to indicate a lighter eye shade. There would be no reasonable inference to be made. Stated another way, it is unpredictable how one would infer natural eye color if half of the SNPs indicated dark eye color and the other half of the SNPs indicated light eye color.

Furthermore, it is unclear how one would infer natural eye color. Rebbeck teaches 7 categories of eye colors, namely blue, gray, green, hazel, light brown, dark brown and black. The specification only analyzes two categories: dark or light.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the association of SNPs with a particular phenotype is unpredictable, it is unclear how one could practice the claimed invention as broadly as claimed. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties in association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection.

The response argues that a total of 10,000 SNPs have been narrowed down to a set of 30-40 SNPs for inferring human eye colors. The response asserts the 30-40SNPs are statistically significant for inferring human eye color (page 8). This

argument is not commensurate in scope with the claimed invention. The claims are directed to the particular 32 SNPs of Table 2. The specification does not provide any evidence for applicants assertion that the SNPs are statistically significant- either individually or in combination.

The response asserts that the specification enables the skilled artisan to genotype a sample and compare the result of the SNP genotyped to infer natural eye color. This argument has been considered but is not convincing because the specification does not provide any results for the panel of 32 SNPs in Table 2. In fact, the specification teaches the delta value (allele frequency differential) was used rather than a p-value because the p-value depends on the sample size. The specification acknowledges that a differential of 10% would be significant with a sample of 500 or so at the 0.05 level but not with a sample of 100. Here the delta value for SEQ ID NO: 3 and 4 is 2% and 11% respectively (see Table 3, page 26). Moreover, the sample size was much less than 100 (21 light and 21 dark eye colored samples) which the specification clearly states a 10% delta would not be significant with a sample of 100. Thus, it is clear that the specification fails to provide any statistically significant results for the skilled artisan to rely upon for inferring natural eye color. Without a significance level of at least 0.05, the results may be due to chance and not a true association that may be relied upon for inferring natural eye color. The response filed March 6, 2011 fails to address the statistical significance discussion above.

Instead, the response argues that the human sequences of selected SNPs do not occur randomly but fall into patterns due to heritage. This argument has been

reviewed but is not deemed persuasive. The specification fails to teach any linkage between the claimed SNPs or any haplotypes involving the SNPs. The response argues that there should not be a "fictional combination" of SNPs such that "all SNPs were not correct". As noted above, there is no evidence or suggestion that the 32 SNPs of Table 2 are completely linked and are in a haplotypes, as argued by the response. The evidence of record would suggest that they are not completely linked since the specification explicitly states that the eye color was correct only when the genotypes of ALL the SNPs were correct.

The response further relies upon Table 2, however, Table 2 does not appear to provide any data of eye shade/alleles. Table 3 provides 10 SNPs and their delta and gene and allele/eye shade, but for the reasons discussed above, there is no significant association that the skilled artisan may reasonably infer natural eye color. It is unclear what the ordinary artisan would infer if SEQ ID NO: 3 was a T and SEQ ID NO: 4 was a G.

The response relies upon Exhibit A, but as discussed above, Exhibit A fails to address each of the SNPs in Table 2 and fails to provide how to infer based upon the SNPs provided in the reference. The response filed April 6, 2011 does not appear to address how the skilled artisan would understand which alleles of SEQ ID NO: 32, 33, 34, for example would be used to compare and infer eye color since the specification is silent with respect to alleles and their association with eye color.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. **No claims allowable.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
May 25, 2011